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CAMPELL, B	
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18M2/0508

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☑ This application has been examined ☑ Responsive to communication filed on 1/23/95 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), — days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☑ Notice of References Cited by Examiner, PTO-892.
2. ☑ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☑ Claims 1-16 are pending in the application.
   Of the above, claims _____ are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☑ Claims 1-16 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☑ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____ ; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

The application should be reviewed for errors. The following error was noted upon examination:

Claim 6, line 7: "phosphoylase"

Please make appropriate correction of this and all similar errors.

Applicant's election with traverse of group II, drawn to *in vivo* methods, in Paper No. 6 is acknowledged. The traversal is on the ground(s) that the same search is required for both groups. This is not found persuasive because, as pointed out previously (paper 5), the two methods require different procedures and reagents, and raise different issues under 35 U.S.C. § 112. The methods are not obvious over each other, as stated previously, and there is nothing in the record to indicate that they are obvious variants. Hence the two methods are patentably distinct.

The requirement is still deemed proper and is therefore made FINAL.

The incorporation of essential material by reference to a foreign application or foreign patent or to a publication inserted in the specification is improper. Applicant is required to amend the disclosure to include the material incorporated by reference. The amendment must be accompanied by an affidavit or declaration executed by the applicant, or applicant's attorney or agent, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. *In re Hawkins*, 486 F.2d 569, 179 USPQ 157; *In re Hawkins*, 486 F.2d 579, 179 USPQ 163; *In re Hawkins*, 486 F.2d 577, 179 USPQ 167.

The attempt to incorporate subject matter into this application by reference to Balhorn et al., Talanian et al., Qlan et al., Ashley et al., Rabindran et al. and Krawetz et al. is improper because none of these references is a U.S. patent or allowed application. The nucleotide sequences encoding DNA-binding domains of proteins (presumably disclosed in these references) are essential to the claimed invention because the compositions of claims 6, 7 and 10-12 can not be made without this information.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to adequately teach how to make and use the invention, i.e. failing to provide an enabling disclosure.

The specification does not adequately teach how to make the claimed compositions. The specification does not disclose the amino acid or nucleotide sequence of any antibody or DNA binding protein suitable for use in the claimed methods. The nucleotide sequences, or at least amino acid sequences from which nucleotide sequences could be deduced, are required to produce the claimed fusion proteins. The specification does disclose sequences of PCR primers used to amplify certain DNA fragments used in the exemplified gene construct. However, there is no indication that the plasmids used as PCR templates are publicly available and would remain available without restriction throughout the term of the patent. Hence there is no assurance that others would be able to make even the exemplified construct. As noted above, Applicants can not rely on incorporation by reference to provide the essential sequence information.

The specification does not adequately teach how to use the claimed compositions and methods for *in vivo* applications. The specification alleges that the disclosed compositions can be used to deliver "therapeutic" polynucleotides, such as toxin-encoding genes, to cells via an endocytotic mechanism. While it is not unreasonable to expect that the transferred polynucleotide would be expressed to some extent (see Wu et al.), it is not clear that a level of expression sufficient to produce any therapeutic effect can be achieved. Curiel et al. teach that the endocytosis method has an important limitation: the endocytosed complexes are targeted to the lysosome, where they are degraded (entire document). Discussing gene transfer by transferrin-polycation conjugates, Curiel et al. conclude that the process "is functionally limited by the absence of specific mechanisms to accomplish conjugate-DNA-complex release from the cellular vesicle system" (p. 8853, last

paragraph). Thus this publication suggests that the claimed antibody-DNA binding protein fusions and methods for their use, like the transferrin-polycation conjugates of Curiel et al., would not be an effective system for nucleic acid transfer *in vivo*. Furthermore, the claims encompass methods in which any and all cell types of an organism are targeted. In fact, it is not known whether the claimed compositions could reach all cell types. For example, the blood-brain barrier would be expected to prevent the compositions from reaching the brain.

Even if it were known that the claimed compositions and methods could be used *in vivo*, the specification still does not adequately teach how to use them for this purpose. Very little guidance is provided regarding dosages, means of administration, frequency of administration, etc. Furthermore, no working examples of *in vivo* use are disclosed.

For the reasons discussed above, it would require undue experimentation for one of ordinary skill in the art to make and use the claimed compositions and processes for delivery of polynucleotides *in vivo*, particularly given the breadth of the claims, the amount of experimentation necessary, the scarcity of guidance and working examples in the specification, and the unpredictable nature of the art.

Claims 1-16 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

Claims 6, 9, 13, 15 and 16 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically:

Claim 6 is indefinite because some of the recited proteins are actually protein families. It is not clear whether all family members are being claimed or only certain members.

Claim 9 is indefinite in its recitation of "flanking...regions" because it is not clear what these regions flank. 01C

Claim 9 is confusing and grammatically incorrect because a word such as "or" or "and" should appear before "a promoter". 01C

Claims 13, 15 and 16 are indefinite and confusing because they use terminology which implies *in vitro* use of the methods, while *in vivo* methods have been elected. Terms such as "medium containing the target cell" and "serum containing a target cell" do not clearly set forth how the claimed compositions are to be administered.

Claims 13, 15 and 16 are vague and indefinite in their recitation of "waiting until..." because it is not clear how long one should wait for the recited event to occur, nor how the event is detected.

Claims 15 and 16 are indefinite because it is not clear what the purposes of the methods are.

Claims 15 and 16 are incomplete because they do not recite a step in which the nucleic acid is delivered into the target cell.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 8 and 9 are rejected under 35 U.S.C. § 102(b) as being anticipated by Beug et al. Beug et al. disclose a nucleic acid carrier molecule consisting of a targeting moiety (transferrin) linked to a nucleic acid binding moiety, complexed with a nucleic acid (entire document). Beug et al. disclose that the carrier molecule can be made as a fusion protein using recombinant techniques, and that any nucleic acid sequence can be bound by the carrier, including ribozymes and retroviral vectors (which would possess long terminal repeat regions) (pp. 8-9).

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

Claims 2-5, 7 and 10-16 are rejected under 35 U.S.C. § 103 as being unpatentable over Beug et al. in view of Chaudhary et al. and Wu et al. Beug et al. disclose a nucleic acid carrier, which is a fusion protein consisting of transferrin fused to a polycationic polypeptide, complexed with a nucleic acid molecule, as discussed above. Beug et al. also suggest the use of protamine as the nucleic acid binding moiety (p. 6) and demonstrate the use of the carrier to transform cells *in vitro* (examples 5-13). Beug et al. do not teach a carrier in which the targeting moiety is an antibody or the nucleic acid encodes *Pseudomonas* exotoxin A (PEA), nor do they demonstrate transformation of cells *in vivo*. Chaudhary et al. disclose a fusion protein which consists of a single chain antibody having a truncated form of PEA (containing domain III) fused to its carboxyl end (p. 1068). This fusion protein is used to deliver PEA specifically to cells expressing the surface antigen recognized by the antibody (entire document). Chaudhary et al. teach a method for cloning antibody genes (entire document), and a method for

producing and purifying the fusion protein (p. 1067). Chaudhary et al. teach that the truncated form of PEA is a potent toxin and disclose a plasmid encoding the truncated PEA (p. 1066, Fig. 5). Chaudhary et al. teach that a fusion protein containing an antibody against the interleukin-2 receptor was used to selectively deliver PEA to cells expressing the receptor (p. 1066). Wu et al. teach a nucleic acid carrier consisting of a cell-receptor specific ligand linked to a polycationic polypeptide (entire document), and demonstrate successful use of this carrier to deliver and express DNA to a specific cell type *in vivo* (by intravenous injection; col. 11). Wu et al. suggest that an antibody could be used as targeting moiety (col. 6, lines 3-7), that protamine could be used as the polycationic polypeptide (col. 4, lines 39-44), and that a peptide bond could be used to link the targeting and DNA binding moieties (col. 5, lines 45-48).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of the prior art to develop the claimed compositions and methods. It would have been obvious to modify the transferrin-polycationic polypeptide fusion of Beug et al. by substituting an antibody for transferrin, given the suggestion of Wu et al. to use an antibody for cell type-specific targeting of DNA and the demonstration of successful cell type targeting with antibodies by Chaudhary et al. It would have been obvious to use protamine as the DNA binding protein, given the suggestion to do so by Beug et al. and Wu et al. It would have been obvious to fuse the DNA binding protein to the carboxyl end of the antibody, since Chaudhary et al. had shown that this arrangement preserved the ability of the antibody to recognize antigen. Having made the antibody-polycationic polypeptide fusion protein by the methods of Chaudhary et al., it would have been obvious to use it to deliver polynucleotides *in vivo* as discussed by Beug et al. and demonstrated by Wu et al. using different targeting moieties. It would have been obvious to deliver a gene encoding PEA, since Chaudhary et

al. had shown this toxin to be extremely potent. One would have been motivated to develop the claimed compositions and methods, given the knowledge that virtually any nucleic acid could be delivered in this manner, as taught by Beug et al., and that use of antibodies would allow targeting of any cell type which produces a cell type-specific antigen. Thus, the invention was clearly *prima facie* obvious as a whole to one of ordinary skill in the art at the time the invention was made.

Claim 6 is rejected under 35 U.S.C. § 103 as being unpatentable over Beug et al. in view of Chaudhary et al. and Wu et al. as applied to claims 2-5, 7 and 10-16 above, and further in view of Ryder et al. Beug et al. in view of Chaudhary et al. and Wu et al. teach fusion proteins, consisting of an antibody fused to a DNA-binding protein, complexed with nucleic acids, as discussed above. Beug et al. in view of Chaudhary et al. and Wu et al. do not teach fusion proteins wherein the DNA-binding protein is one of those recited in claim 6. Ryder et al. disclose the amino acid sequences of the DNA-binding regions of three *jun* proteins (Fig. 2) and the nucleotide sequence of *jun-D* cDNA (Fig. 1).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize one of the *jun* sequences disclosed by Ryder et al. as the DNA-binding moiety of the fusion protein of Beug et al. in view of Chaudhary et al. and Wu et al. One would have expected the *jun* protein to be effective, since it was known to bind certain DNA sequences. Thus, the invention was clearly *prima facie* obvious as a whole to one of ordinary skill in the art at the time the invention was made.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bruce Campell, whose telephone number is 703-308-4205. The examiner can normally be reached on Monday-Thursday from

8:30 to 5:00 (Eastern time). The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jacqueline Stone, can be reached on 703-308-3153. The FAX phone number for art unit 1804 is 703-308-4312.

An inquiry of a general nature or relating to the status of the application should be directed to the group receptionist whose telephone number is 703-308-0196.

BC

Bruce Campell
April 19, 1995

JACQUELINE M. STONE
SUPERVISORY PATENT EXAMINER
GROUP 1800